

Survival and Reproduction Among Males With Birth Defects and Risk of Recurrence in Their Children

Rolv T. Lie, PhD

Allen J. Wilcox, MD, PhD

Rolv Skjærven, PhD

AFATHER'S CONTRIBUTION TO his children's risk of birth defects is not well established. If the father has a birth defect, he may pass on to his children genes that increase their risk of a birth defect. However, the extent to which children of affected males are at higher risk is unknown except in a few specific types of birth defects. Furthermore, if a father has a particular birth defect, it is unknown whether his offspring are at increased risk of having any other kinds of birth defects.

We observed a cohort of nearly a half million males from birth to adulthood, using a population-based registry in Norway. Males with registered birth defects were compared with other males regarding survival, their probability of having offspring, and risk of birth defects in their offspring. We have previously reported similar data for a cohort of females with birth defects.¹

METHODS

Population-Based Cohort

The population-based Medical Birth Registry of Norway records all births in Norway since 1967 (about 1.8 million births). All live births and stillbirths at a gestational age of at least 16 weeks are included in the registry. There were 486 207 live and stillborn male infants delivered in Norway between 1967 and

Context Few systematic data exist on survival and reproduction among males with birth defects and their contribution to occurrence of birth defects in the next generation.

Objective To estimate survival of males with registered birth defects, their subsequent reproduction rates, and their risk of transmitting birth defects to their offspring.

Design and Setting Population-based cohort study of data from the Medical Birth Registry of Norway.

Subjects A total of 486 207 males born in Norway between 1967 and 1982, 12 292 of whom had a recorded birth defect.

Main Outcome Measures Survival rates through 1992, reproduction rates through 1998, and risk of birth defects among offspring of males with vs without birth defects.

Results Survival through 1992 was lower among males with birth defects (84% vs 97%). Compared with males without birth defects, affected males were 28% less likely to have had a child. Among offspring of affected males, 5.1% had a registered birth defect compared with 2.1% of offspring of males without birth defects (relative risk [RR], 2.4; 95% confidence interval [CI], 1.9-3.0). Offspring of affected fathers had an increased risk of the same defect as their fathers (RR, 6.5; 95% CI, 4.0-10.4) and an increased risk of dissimilar defects (RR, 1.8; 95% CI, 1.3-2.5).

Conclusions Compared with unaffected males, males with birth defects have higher mortality and survivors are less likely to have a child. Fathers with birth defects are significantly more likely than unaffected fathers to have an affected child.

JAMA. 2001;285:755-760

www.jama.com

1982, which we defined as our study cohort. In our analyses, the cohort was divided into those with a registered birth defect (n=12 292 males [2.5%]) and the remaining males without birth defects (the reference group). The cohort was followed up for survival through 1992, when the most recent linkage with mortality records was carried out, and for reproduction through September 1998.

Linking Fathers and Offspring

The Medical Birth Registry of Norway includes unique personal identification

numbers for all births in Norway as well as the identification number of the father and mother. These identifiers permit linkage of males born early in the cohort with their offspring born later (1983-1998). This linkage does not ensure 100% detection of the cohort's offspring. During the

Author Affiliations: Section for Medical Statistics and Medical Birth Registry of Norway, University of Bergen, Norway (Drs Lie and Skjærven); and the National Institute of Environmental Health Sciences, Research Triangle Park, NC (Dr Wilcox).

Corresponding Author and Reprints: Rolv T. Lie, PhD, Section for Medical Statistics, University of Bergen, Armauer Hansens Bldg, 5021 Bergen, Norway (e-mail: Rolv.Lie@smis.uib.no).

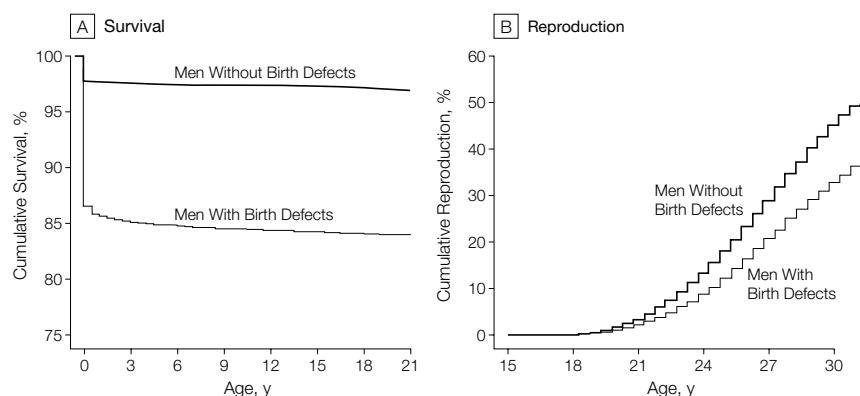
Table 1. Male Births, Survival, and Reproduction

Year of Birth	Births	Age at End of Follow-up, y*	Survival, No. (%)†	Reproduction, No. (%)‡
1967-1969	105 324	28-31	100 399 (95.3)	46 170 (46.0)
1970-1972	101 518	25-28	97 357 (95.9)	26 415 (27.1)
1973-1975	92 076	22-25	88 967 (96.6)	10 272 (11.5)
1976-1978	81 152	19-22	78 973 (97.3)	2445 (3.1)
1979-1982	106 137	15-19	103 620 (97.6)	272 (0.3)
Total	486 207	15-31	469 316 (96.5)	85 574 (18.2)

*Follow-up was completed through September 1998.

†Survival was followed up through 1992.

‡Reproduction data are expressed as the percentage of survivors who became fathers by September 1998.

Figure 1. Survival and Reproduction Among Males Born With and Without Birth Defects

The cohort was followed up for survival through 1992 and for reproduction through September 1998. Reproduction data were analyzed only among survivors.

later period, 5.6% of the births lacked a father's identity and, therefore, were excluded from this analysis. The lack of identified fathers was associated with fetal death; the percentage of stillbirths that did not have an identified father was 51%. Also, younger mothers were more likely to have children with an unidentified father, which presumably led to selective loss of recorded births for younger fathers. Finally, children born outside of Norway to Norwegian-born parents are not captured by the registry (although outmigration during this period was extremely low²). By 1998, the registry had accumulated 110 327 births that could be linked to fathers born in the study cohort.

Classification of Birth Defects

The Medical Birth Registry of Norway records birth defects that are diagnosed at delivery or by pediatric examination during the initial hospitaliza-

tion (≥ 5 days). In this study, 24 categories of birth defects were used, the same as in 2 previous studies.^{1,3} Categories of birth defects were based on the 3-digit codes of the *International Classification of Diseases, Eighth Revision* (ICD-8), with minor modifications. Most of the birth defects included are major; however, minor defects may be included in some categories and cannot be distinguished by ICD-8 codes. For example, the heterogeneous category of limb defects includes serious reduction deformities and, possibly, minor soft-tissue syndactylies.

Most affected children had only 1 specific birth defect diagnosis. Cases with multiple defects were pooled in a separate category, except that when spina bifida was present with anencephaly, only anencephaly was counted, and when hydrocephalus was present with spina bifida, only spina bifida was counted. Isolated cleft palate was sepa-

rated from the 3-digit ICD-8 code for cleft lip and palate as a distinct category. Similarly, Down syndrome was separated as a category distinct from other syndromes.

The Medical Birth Registry of Norway, like other registries based on routine medical birth records, does not capture all birth defects. Estimates of ascertainment vary by defect category. For example, the Medical Birth Registry of Norway captures an estimated 80% of cleft lip and an estimated 60% of Down syndrome cases.⁴ The Norwegian Health Inspectorate has instructed that therapeutic abortions should be reported to the registry as stillbirths, including information on any diagnoses of birth defects. The completeness of such reporting is not known, however.

In analyzing the risk of birth defects in children whose fathers also had birth defects, we defined a *similar* defect as one in the same ICD-8 category as the father's and *other* defects as all others.³

Analysis

Males with birth defects were compared with males without birth defects. Survival and reproduction were based on standard actuarial life-table methods (6-month intervals). Reproduction among males with specific birth defects was calculated as a ratio relative to males who had no reported birth defects, with the inherent limitation of a slight underascertainment of offspring. Estimates of reproduction are based on all males surviving to age 15 years. The 95% confidence interval (CI) for relative reproduction between groups was calculated using a Cox proportional hazards model.⁵

The expected number of birth defects in offspring of fathers with a specific defect was based on risk of birth defects among offspring of males without recorded birth defects. Relative risks (RRs) of recurrence of similar or dissimilar birth defects (the observed-expected ratio [O/E]) were summarized across all paternal defect categories using a stratified approach. Exact *P* values and 95% CIs were calculated using StatXact.⁶

RESULTS

The prevalence of registered defects at birth (including stillbirths) was 2.5% in this cohort of 486 207 males. Eighteen percent (n=85 574) of survivors had at least 1 recorded offspring by September 1998 (TABLE 1). The percentage who had become fathers increased with age, reaching 46% by age 28 to 31 years.

Survival and Reproduction Among Males With Birth Defects

FIGURE 1A shows survival for males with and without birth defects. Males with a birth defect had lower survival to age 20 years (84% compared with 97%, including all male fetuses aged ≥ 16 completed weeks' gestation). Affected males had higher mortality at all ages up to 14 years, with the highest RR in the first year of life (TABLE 2).

If they survived, males with birth defects were less likely than other males to have a child at any age (Figure 1B). Using a Cox regression model, the rate of reproduction among surviving males with birth defects was estimated to be 72% of the reproduction rate among unaffected males (95% CI, 68%-77%). Taking into account both the higher mortality rates and the lower reproduction rates among survivors, a male with birth defects was, on average, only 63% as likely to reproduce by age 30 years as an unaffected male.

FIGURE 2 shows total survival for each of the 24 birth defect categories and reproduction among males in each category relative to unaffected males. The defects that were least likely to cause death were also least likely to reduce a man's probability of having a child if he survived. However, some birth defect categories with high survival rates had substantially reduced reproduction rates and vice versa.

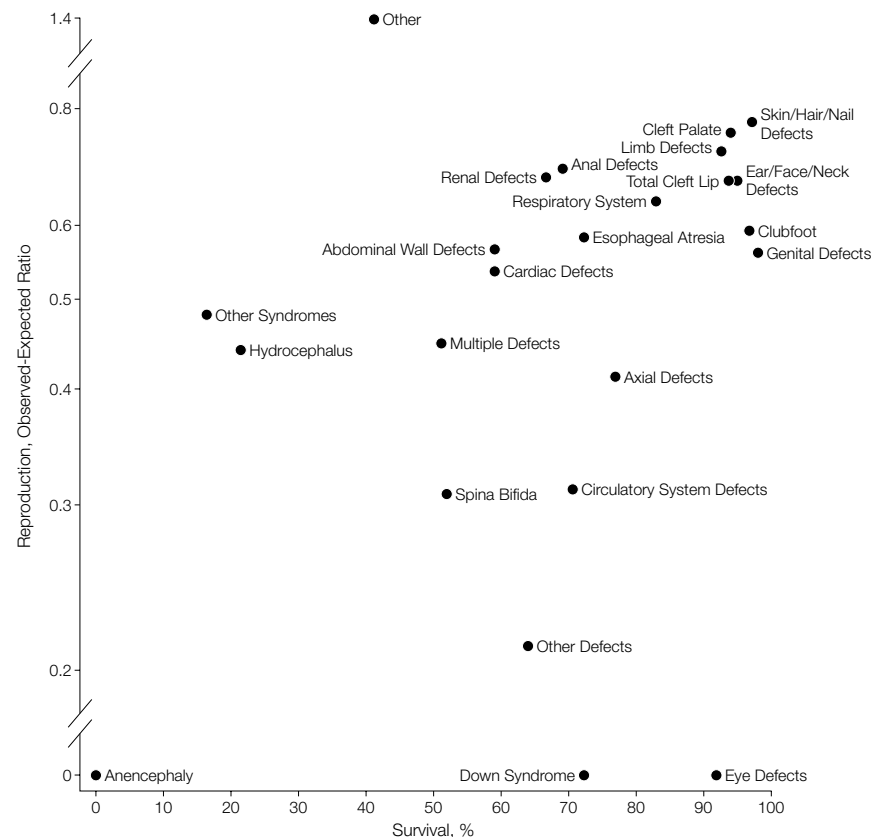
Birth Defects in the Second Generation

Of the 12 292 males with birth defects, 850 had a total of 1265 children. Sixty-four (5.1%) of these children had birth defects. Fathers without birth defects had a total of 109 162 children, of whom 2326 (2.1%) had birth defects.

Table 2. Age-Specific Death Rates of Males With vs Without Birth Defects

Age at Death, y	Death Rates per 1000 Births		Relative Risk (95% Confidence Interval)
	With Birth Defects	Without Birth Defects	
Stillborn	45.4	12.5	3.6 (3.3-3.9)
1	96.7	10.4	9.3 (8.7-9.9)
2	4.1	0.9	4.6 (3.3-6.2)
3-4	4.5	1.3	3.4 (2.5-4.5)
5-9	5.9	1.8	3.2 (2.5-4.2)
10-14	3.2	1.0	3.1 (2.2-4.4)
≥ 15	3.6	3.8	0.9 (0.7-1.3)

Figure 2. Survival and Reproduction of Males Born With Birth Defects by Defect Category



Defect-specific reproduction is reported relative to reproduction of males without birth defects. Reproduction data were analyzed only among survivors.

Thus, the overall risk of a birth defect was 2.4 times higher among children of affected fathers (95% CI, 1.9-3.0). This higher risk of birth defects did not differ by sex of the offspring ($P=.79$).

The excess contribution made by affected fathers to occurrence of birth defects in the next generation was a combination of 2 factors: the proportion of fathers who had birth defects and the

increased risk of defects in their children. Measured in attributable risk,⁷ affected fathers contributed 16 of 1000 registered birth defects in the next generation.

Similarity of Defects in Fathers and Children

TABLE 3 shows the risk of similar and dissimilar birth defects among off-

spring of affected fathers. Twenty-one children had the same defect as their fathers compared with an expected number of 3.2. The most common recurring defects were cleft lip, genitalia defects, limb defects, and clubfoot. The recurrence risk (O/E) was 38-fold for cleft lip, 3.8-fold for genitalia defects, and 12-fold for limb defects. The recurrence risk for clubfoot was 3.4-fold but was not significantly different from 1. The pooled RR for similar defects in children was 6.5 (95% CI, 4.0-10.4).

Forty-three children had defects different from the father's compared with an expected number of 23.7. The O/Es for specific defects were all greater than 1 and, for 2 categories (cleft lip and abdominal wall), this increase was statistically significant. The pooled O/E for a dissimilar defect was 1.8 (95% CI, 1.3-2.5).

COMMENT

The Medical Birth Registry of Norway is a population-based registry that permits follow-up of persons born since 1967. In a previous article, we identified a cohort of females born between 1967 and 1982 and compared the survival and reproduction of females with and without birth defects.¹ In the present article, we provide similar data for males with and without birth defects.

Males with birth defects had higher mortality than unaffected males through infancy and childhood. This

surprising persistence of mortality risk presumably reflects the ongoing complications related to their defects.

Males with birth defects were 28% less likely than unaffected males to have a child. This presumably reflects social as well as biological consequences of their defects. The reduced probability of fathering a child varied substantially across defect categories, with all but the small category of other central nervous system defects having a reduced tendency to reproduce.

The total risk of birth defects was 5.1% among offspring of fathers with defects and 2.1% among offspring of fathers without defects, for an RR of 2.4. No single category of defect explained the higher risk in affected fathers' offspring.

As expected, the risk of birth defects in offspring was increased mainly for the same type of defect as the father's. Fairly precise estimation of the recurrence risk was possible for the most common types of defects. A recurrence risk of the same defect is consistent with a shared genetic etiology, although shared environmental causes cannot be ruled out. Offspring of affected fathers also had an increased risk of dissimilar defects of all types. The explanation for this excess is not as clear, and the possibility of bias must be considered.

The Medical Birth Registry of Norway, like other registries based on rou-

tine medical birth records, does not capture all birth defects. Some are simply underregistered at birth.⁴ Others, such as defects of the heart or kidney, are often ascertained too late to be captured by the registry. This is reflected in the relatively low number of such defects in our data.

Underregistration creates an opportunity for bias. A father's birth defect may make it more likely that a birth defect in his offspring would be recorded in the medical record. If so, we would predict that, on average, these recorded defects would tend to be milder. This was apparently not the case. Among the 64 affected offspring of affected fathers, 9.4% died within the first year of life, while among the 2326 affected offspring with unaffected fathers, only 5.9% died in the first year. It appears that affected offspring of affected fathers had more serious defects compared with affected offspring of unaffected fathers. A tendency for more minor defects to be ascertained in offspring of affected fathers is possible but could not be demonstrated.

Our previous analysis of affected mothers provides some further information on the issue of selective diagnosis. Previously, we found no increase among the offspring of affected mothers in the RR for dissimilar defects.¹ An increased ascertainment of defects would presumably occur among offspring regardless of which parent was

Table 3. Risk of Similar and Dissimilar Birth Defects in Offspring, by Birth Defect Categories of Fathers

Categories*	Fathers, No.	Offspring at Risk, No.	Total Observed Defects in Offspring, No.	Similar Defects			Dissimilar Defects		
				Observed, No.	Expected, No.	Observed-Expected Ratio (95% CI)†	Observed, No.	Expected, No.	Observed-Expected Ratio (95% CI)†
Cleft lip	68	115	12	6	0.16	38 (14-93)	6	2.29	2.6 (1.0-6.1)
Abdominal wall defects	12	15	3	0	0.004	0 (0-1243)	3	0.32	9.5 (2.1-43)
Clubfoot	218	316	10	4	1.17	3.4 (0.9-9.0)	6	5.57	1.1 (0.4-2.4)
Limb defects	123	184	9	3	0.25	12 (2.5-37)	6	3.67	1.6 (0.6-3.7)
Genital defects	246	370	17	5	1.31	3.8 (1.2-9.2)	12	6.58	1.8 (0.9-3.3)
Anal defects	11	14	2	1	0.006	173 (4.3-1290)	1	0.29	3.4 (0.08-24)
Skin/hair/nail defects	29	42	2	1	0.029	35 (0.87-215)	1	0.87	1.2 (0.03-6.8)
Multiple defects	35	61	4	1	0.17	5.9 (0.2-35)	3	1.13	2.7 (0.5-8.4)
Total defects	850	1265	64	21	3.22	6.5 (4.0-10.4)	43	23.7	1.8 (1.3-2.5)

*Only categories with at least 2 occurrences in offspring are shown.

†Fathers without the specific defect were the reference. CI indicates confidence interval.

affected. Thus, we observed no evidence to support ascertainment bias as the reason for an excess of dissimilar defects among offspring of affected fathers.

If male neonates are routinely inspected more closely for defects than female neonates, this could lead to ascertainment of more minor defects for males within each defect category. If such minor defects had a stronger tendency to result in a dissimilar defect in offspring, this could contribute to a higher risk in offspring of affected fathers. Some children with 1 registered birth defect probably also have other unascertained birth defects. If such underascertainment were more frequent for males, this also could lead to an increased risk of apparently dissimilar defects.

Although the recurrence risk from father to offspring was substantial, the number of affected fathers was too low to contribute many birth defects to the next generation. Only 1.6% of birth defects in the second generation could be attributed to a defect in fathers. Males with birth defects were slightly more likely than other males to find a partner with a birth defect (1.6% vs 0.9%). However, this difference is too small to explain the excess risk of dissimilar defects. Of the 15 pairs of parents in which both had birth defects, only 1 had an affected child (father, mother, and child all had cleft lip).

Given the structure of the cohort (comprising all male births in 1967-1982), only a small proportion of the members of the cohort have reached age 31 years. Caution must be used in making longitudinal interpretations of these cross-sectional data. A complete reproductive history will be required to make a more definitive inference about male reproduction and risk of birth defects in offspring.

This study had incomplete ascertainment of offspring among males in the cohort. During the period when these births occurred, nearly 6% of birth certificates had no recorded father and, as a consequence, some males in the cohort became fathers without evidence in the registry. Since the father's information was

lacking for half of stillbirths, and children with birth defects are more likely than others to be stillborn, the total number of children with birth defects born to the study cohort of males is probably underascertained.

Furthermore, offspring of affected fathers may be selectively underascertained to the extent that these offspring more often have birth defects and, therefore, more often are stillborn. The effect could be that we slightly underestimate the fertility of affected fathers and, more importantly, that we may underestimate the percentage of birth defects among their offspring.

For an unknown percentage of birth certificates, the recorded father is not the biological father. Such errors would reduce the contrast in rates of recurrence between affected and unaffected males.

Our estimates of recurrence risk do not take into account the slight statistical dependence of outcomes within the family structure, ie, that some fathers are represented with more than 1 child.⁸ While this may widen some CIs, the effects are minimal and should have little or no impact on the risk estimates themselves. The results were similar when analyses were restricted to only 1 (the first) child per father.

There are similarities but also apparent dissimilarities between these data for males and the data for females reported previously.¹ Birth defects generally were more prevalent among males than females. This male excess of defects also has been observed in other cohorts.⁹

Infant and childhood mortality rates were lower for affected males than for affected females (16% vs 20%).¹ This counters the usual survival advantage of females in infancy and childhood. The higher mortality for affected females was not explained by any specific category of defects. Given the higher rate of recorded defects among males, it is possible that less severe manifestations of a given defect are more likely to be registered for males than for females.

The 28% reduced reproduction tendency among affected males is very

similar to the reduction previously seen among affected females (27%).¹ Given that reproduction is a more complex function for mothers than for fathers, we might have expected a smaller reduction among affected males. Similarly, if the excess birth defects among males reflect the selective recording of a greater number of milder defects, we might have expected less reproductive impairment among males than females. Neither was the case.

Affected males were slightly more likely than affected females to contribute offspring to the next generation (63% vs 60%). Given that more males than females had registered birth defects, there were substantially more affected fathers than affected mothers contributing to the next generation. This result was not fully apparent at the follow-up in 1998 because males tend to become parents later in life than females, and the present data are truncated at a relatively young age.

The RR for birth defects among offspring was significantly higher for affected males (2.4) than for affected females (1.6) (test of homogeneity of odds ratios, $P=.03$). This difference hypothetically may be explained by a greater contribution of paternal genes to risk of birth defects (genomic imprinting).

The pooled RR of a woman having a child with the same defect was 6.8,¹ similar to the father's risk of 6.5. However, affected mothers had no apparent increase in risk of offspring with other defects (RR, 1.0),¹ in contrast with the substantial increase in the father's risk of other defects (RR, 1.8). The higher risk of dissimilar defects with affected fathers apparently accounts for the entire excess of birth defects among offspring of affected fathers compared with offspring of affected mothers. A syndrome could hypothetically be expressed as different defects in different affected family members. It is unclear whether this could explain a higher tendency of males to pass on a different defect to the next generation.

There are few data in the literature that compare recurrence risk for fathers and mothers, and these data are

restricted to recurrence of the same defect carried by the parent. Mothers have been reported to be more likely than fathers to pass on a heart defect to a child.^{10,11} In a study of spina bifida, mothers of affected children were more likely than fathers to report a family history of spina bifida.¹² The authors interpret this as evidence of preferential transmission of these defects through females, although this could also be because of more complete reporting by mothers.

Affected males contributed more affected offspring than affected females, not merely because of their increased risk of having affected offspring but because there were more affected fathers

than mothers. The attributable risk of birth defects in the next generation from affected fathers was 3 times that from affected mothers (1.6% vs 0.5%).¹ The sum of 2 attributable risks is usually an overestimate of their total, so the combined contribution from affected parents is presumably no more than 2%.

In this report, we have shown that males with birth defects have increased mortality throughout childhood compared with unaffected males and that males with birth defects are less likely to have a child. Furthermore, our data suggest that fathers with birth defects are significantly more likely than unaffected fathers to have children with birth defects. In many respects, these

findings are similar to previously published data for females. However, affected fathers appear to contribute more birth defects than affected mothers to the next generation.

Author Contributions: Dr Lie participated in study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical expertise.

Dr Wilcox participated in study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and medical expertise.

Dr Skjærven participated in study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical expertise.

Acknowledgment: We are indebted to Donna D. Baird, PhD, Olga Basso, PhD, Ruth Little, ScD, and Stein Emil Vollset, MD, DrPH, for helpful comments.

REFERENCES

1. Skjærven R, Wilcox AJ, Lie RT. A population-based study of survival and childbearing among female subjects with birth defects and the risk of recurrence in their children. *N Engl J Med*. 1999;340:1057-1062.
2. *Population Statistics 1994: Volume III, Survey*. Oslo, Norway: Statistics Norway; 1995.
3. Lie RT, Wilcox AJ, Skjærven R. A population-based study of the risk of recurrence of birth defects. *N Engl J Med*. 1994;331:1-4.
4. Lie RT, Heuch I, Irgens LM. Maximum likelihood estimation of the proportion of congenital malformations using double registration systems. *Biometrics*. 1994;50:433-444.
5. Norusis MJ. *SPSS for Windows: Advanced Statistics, Version 6.0* [computer program]. Chicago, Ill: SPSS Inc; 1993.
6. Metha C, Patel N. *StatXact for Windows* [computer program]. Cambridge, Mass: Cytel Software; 1999.
7. Rothman KJ. *Modern Epidemiology*. Boston, Mass: Little Brown; 1986.
8. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986; 42:121-130.
9. Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations: analysis of epidemiologic factors in congenital malformations: report from the Collaborative Perinatal Project. *Birth Defects Orig Artic Ser*. 1975;11:1-22.
10. Nora JJ, Nora AH. Maternal transmission of congenital heart disease: new recurrence figures and the question of cytoplasmic inheritance and vulnerability to teratogens. *Am J Cardiol*. 1987;59:459-463.
11. Burn J, Brennan P, Little J, et al. Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. *Lancet*. 1998;351:311-316.
12. Chatkupt S, Lucek PR, Koenigsberger MR, Johnson WG. Parental sex effect in spina bifida: a role for genomic imprinting? *Am J Med Genet*. 1992;44: 508-512.